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Armanni-Ebstein phenomenon and hypothermia

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ABSTRACT

Retrospective review was undertaken of 46 cases of lethal hypothermia for the presence of subnuclear vacuolization of renal tubular epithelial cells. Fifteen of the 46 cases (33%) had renal tubular vacuolization typical of the Armanni-Ebstein phenomenon. The age range was 30–87 years (average 59 years) with a male to female ratio of 6:9. Nine of the 15 cases with Armanni-Ebstein changes (60%) had a history of diabetes mellitus, and in seven of these vitreous humour biochemical analyses were performed, all of which revealed diabetic ketoacidosis (vitreous glucose levels = 32.9–85.3 mmol/L; β-hydroxybutyrate = 7.4–20 mmol/L). This study has confirmed the association between hypothermia and renal tubular epithelial vacuolization, but in addition raises the prospect that this may be contributed to in some cases by underlying diabetic ketoacidosis. Hypothermic deaths should, therefore, raise the possibility of diabetes mellitus and initiate postmortem biochemical measurement of vitreous humor glucose and β-hydroxybutyrate levels.

1. Introduction

Armanni-Ebstein is the term used to describe subnuclear vacuolization of renal tubular epithelial cells that is most often seen in poorly controlled diabetic states. Debate has occurred as to whether the accumulated material consists of glycogen or lipid, with recent data supporting the latter [1–3]. In addition to diabetes mellitus, renal tubular vacuolization has also been reported in cases of lethal hypothermia. The following study was undertaken to further investigate this association.

2. Materials and methods

Case files from Forensic Science SA, Adelaide, Australia were retrospectively reviewed over a six-year period from April 2004 to March 2010 for cases where deaths were due to, or contributed to, by hypothermia. All cases had undergone full police and coronial investigations with complete autopsy examinations being performed. Hypothermia had been diagnosed when there was a recorded antemortem core temperature less than 30 °C, or if erosive gastritis with so-called Wischnewsky spots was found at autopsy in an individual who had been alone for some time in a cool environment.

Autopsy reports were reviewed and the age, gender and pathological findings were summarized. Specific details of diabetic status, blood alcohol concentration and the results of vitreous biochemistry, if performed, were recorded. Histological sections of the kidneys were then examined for the presence of Armanni-Ebstein lesions. Cases where putrefaction and autolysis precluded accurate histological assessment were excluded from the series.

3. Results

A total of 62 cases with terminal hypothermia were identified, 16 of which were excluded due to poor renal preservation. Of the remaining 46 cases, Wischnewsky spots were present in 44 (96%) and antemortem core temperatures were taken in 7 cases (ranging from 22.5 to 29.7 °C). Blood alcohol levels were measured in 31 cases ranging from 0 to 0.19%, with a mean of 0.02%. Fifteen of the 46 cases (33%) had renal tubular vacuolization typical of the Armanni-Ebstein phenomenon (Fig. 1). PAS/PAS-D staining did not reveal glycogen, although oil-red O staining and electron microscopy (Fig. 1 inset and Fig. 2) demonstrated lipid droplets. The age range was 30–87 years (average 59 years) with a male to female ratio of 6:9. Blood alcohol levels were measured in five of these cases and were negative. Nine of the 15 cases with Armanni-Ebstein changes (60%) had a documented medical history of diabetes mellitus; in the remaining six cases the clinical history was unknown and vitreous humour biochemical analyses had not been performed. Of the nine cases with a known history of diabetes mellitus, five had nodular glomerulosclerosis and seven had vitreous humour biochemical analyses performed, all of which revealed diabetic ketoacidosis (vitreous glucose levels = 32.9–85.3 mmol/L; β-hydroxybutyrate = 7.4–20 mmol/L); this was not tested for in the remaining two cases (Fig. 3). The postmortem interval when vitreous humor was withdrawn ranged from 2 to 6 days, mean 5.2 days.

A total of 31 of the 46 cases (67%) did not have Armanni-Ebstein lesions. The ages ranged from 38 to 89 years (average 69.23 years) with a male to female ratio of 13:18. A history of diabetes mellitus had been documented in four cases (13%) and was unknown in the

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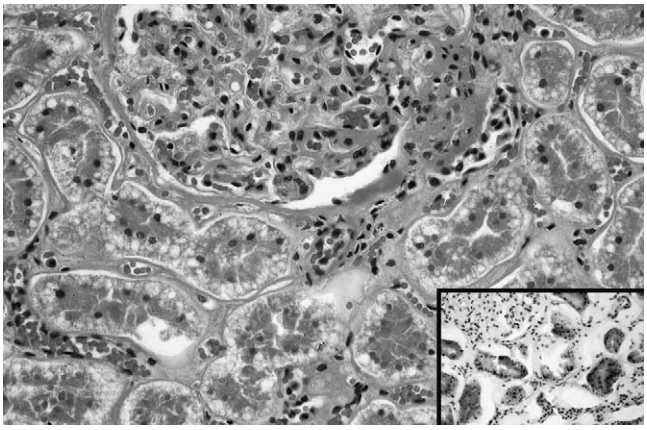

Fig. 1. Characteristic subnuclear vacuolization of renal tubular epithelial cells in a case of hypothermia and ketoacidosis (hematoxylin & eosin ×100). Inset shows patchy oil-red O staining of lipid droplets within tubular epithelial cells (×60).

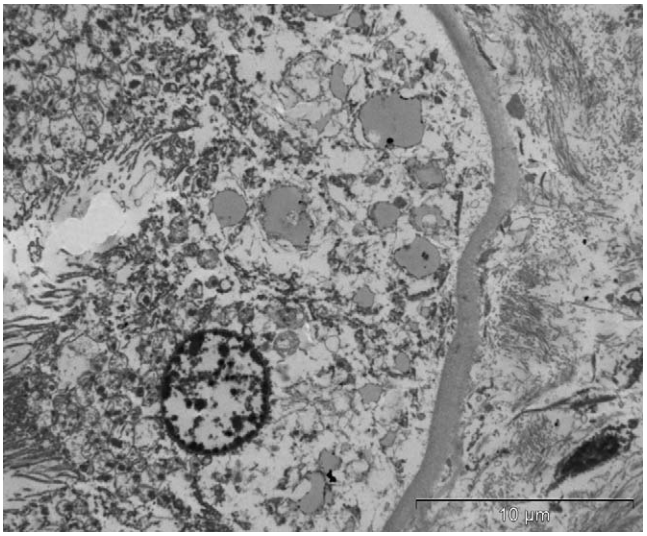

Fig. 2. Electron microscopy of the case shown in Fig. 1 demonstrating intraepithelial lipid accumulation.

remaining 27 cases. Diabetic ketoacidosis had not been tested for at autopsy.

Only one of the victims who had antemortem core temperatures taken (indicating survival for some time) had Armanni-Ebstein changes, and this was a woman who had died of diabetic ketoacidosis with significantly elevated glucose (47.6 mmol/L) and β-hydroxybutyrate (8.87 mmol/L) levels, and no detectable blood alcohol (Brief details of this case have been previously reported [4]). Deaths in the remaining six cases were due to: ischemic heart disease and dementia, ischemic heart disease, subdural hemorrhage, epilepsy and cardiomegaly, and bronchopneumonia ($N = 2$).

4. Discussion

Hypothermia results from the body core temperature falling to less than 35 °C and occurs when counter-regulatory mechanisms such as vasoconstriction and heat production are exceeded by heat loss to the environment [5,6]. Hypothermia is a significant event and has been associated with greater than 70% mortality when the core temperature drops to 30 °C, and 90% at 26 °C. Lethal mechanisms include ventricular fibrillation or asystole, contributed to by myocardial ischemia, hypoxia, electrolyte abnormalities, and elevated catecholamine levels [5].

The most common cause of severe hypothermia is accidental exposure to low ambient temperatures associated with a number of exacerbating factors such as damp conditions, air movement, inadequate or wet clothing, low muscle mass, alcohol ingestion and alcoholism, certain medications and drugs, trauma, open injuries, immobility, neurological, endocrine and cardiovascular disorders, and psychiatric illness [7]. Children and the elderly are at highest risk [5].

Erosive gastritis or Wischnewsky spots are present in 40–90% of fatal hypothermia cases, but this may be artificially high if this finding has been used as a diagnostic parameter, as in the current series. The lesions consist of superficial gastric erosions characterized histologically by necrosis of the mucosa with acid hematin formation. Acute pancreatitis with hemorrhage and surrounding fat necrosis may also rarely be present [5,6].

Fatty changes on routine histology have been associated with fatal hypothermia, with vacuolization of hepatocytes and cardiac myocytes occasionally being documented [6]. In terms of renal tubules, Preuβ et al. demonstrated basal vacuolization of tubular epithelial cells in 87% of cases of terminal hypothermia leading to the conclusion that these changes represented "a very reliable histologic diagnostic criterium in cases of hypothermia, comparable to the significance of Wischnewsky ulcers" [8]. The vacuoles stain positively for lipids and are morphologically similar to Armanni-Ebstein lesions that are strongly associated with poorly controlled diabetic states and deaths due to diabetic ketoacidosis [9,10]. While the vacuoles in Armanni-Ebstein lesions complicating diabetes were initially thought to contain to glycogen [9–13], recent studies have demonstrated positive staining for lipids, suggesting that the vacuoles consist of accumulated triglycerides [1–3]. Occasionally the vacuolization may be so profound that it can be observed macroscopically as cortical pallor [4]. In our series, a case of hypothermia and diabetic ketoacidosis demonstrated lipid on both histological staining and on electron microscopy (Figs 1 and 2).

Although it has been asserted that "fatty degeneration of renal tubules cannot be regarded as a sign of diabetes" [8], it is unclear from this study what the levels of glucose and β-hydroxybutyrate were. Certainly while many individuals with a history of diabetes mellitus do not manifest Armanni-Ebstein phenomenon, due to lack of terminal ketoacidosis, others do [1–3,9–14]. Thus, as the renal tubular vacuoles in hypothermia and in diabetic ketoacidosis appear similar in morphology and composition, the current study

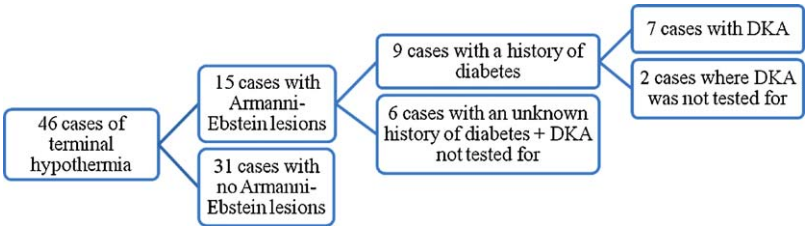

Fig. 3. An analysis of 46 cases with hypothermia showing the number of cases with Armanni-Ebstein phenomenon and the relationship to diabetes mellitus and ketoacidosis (DKA) on vitreous humor testing.

was undertaken to ascertain whether there might be a relationship between cases of hypothermia with Armanni-Ebstein phenomenon, and diabetes mellitus, as has been suggested in a case report that was not included in the present series [15].

The diagnosis of Armanni-Ebstein phenomenon at autopsy may be difficult if there has been significant putrefaction and/or autolysis, as this may cause nonspecific cytoplasmic vacuolization and artefactual separation of proximal tubular epithelial cells from the basement membrane, features that resemble Armanni-Ebstein lesions. This may be predisposed to in hypothermic deaths when there has been social isolation and delay in finding the victim, as this may enhance putrefactive changes [16].

The present study has shown that more than half of the cases of terminal hypothermia where Armanni-Ebstein change was observed (60%) had an established history of diabetes mellitus. This may well be a significant underestimation, as a history of diabetes mellitus may not have been volunteered in the remaining cases, and so vitreous biochemical testing was not routinely undertaken. Significantly, of the nine known diabetic victims with Armanni-Ebstein lesions, all who were tested ($N = 7$) had biochemical evidence of diabetic ketoacidosis. This suggests that renal tubular epithelial vacuolization in cases of hypothermia may have a significant association with diabetic ketoacidosis.

In turning to the literature, there is certainly a recognized association between diabetes mellitus and hypothermia, with diabetic individuals being more susceptible to dropping their core temperature [7] resulting in hospital admissions for hypothermia being more common among diabetic patients compared to the general population [17,18]. This may be influenced by the greater frequency of pathological conditions that are associated with an increased risk of hypothermia among the diabetic population, such as other endocrinopathies [18]. Autonomic neuropathy, which is a common complication of diabetes mellitus, also places individuals at increased risk of developing hypothermia due to impaired physiologic thermoregulatory mechanisms, including peripheral vasoconstriction [17,19,20].

Metabolic complications of diabetes mellitus can cause secondary hypothermia. For example, hypoglycaemia may result in increased heat loss from sweating, inhibition of shivering, and peripheral vasodilation [17–19]. Hypothermia may also be a cause and a complication of diabetic ketoacidosis [21] with Gale and Tattersall reporting diabetic ketoacidosis as the basis for 11.8% of all hospital admissions for severe hypothermia; a rate higher than that for hypothyroidism (8%) [22]. Acidosis can interfere with thermoregulation and cause peripheral vasodilation with a reduced ability to maintain core body temperature when exposed to cold ambient temperatures [23,24]. Insulin deficiency in diabetic ketoacidosis also decreases the uptake of glucose into muscles and adipose tissue, leading to decreased substrate availability for heat production and impaired chemical thermogenesis [7,21,23].

A reverse relationship between hypothermia and diabetes mellitus also exists as primary hypothermia can worsen a decompensated diabetic state. When the core temperature decreases below 32 °C, insulin activity and release are both markedly reduced, resistance to exogenous insulin develops, and peripheral utilization of glucose declines. Additionally, there is also increased secretion of catecholamines and cortisol during hypothermic states, which exacerbate diabetic ketoacidosis [7,22,24]. Consequently, concurrent hypothermia and diabetic ketoacidosis may initiate a vicious metabolic cycle associated with a high mortality rate exceeding 30% [25].

Although in the current study, Armanni-Ebstein lesions were found in only approximately a third of cases with terminal hypothermia, considerably less than other studies [8], the association between renal tubular epithelial vacuolization and hypothermia was confirmed. While the numbers in the study are relatively small and the review was retrospective, a history of diabetes mellitus was recorded in autopsy files in over a half of those with Armanni-Ebstein changes, and all of those from this group who were tested exhibited biochemical evidence of diabetic ketoacidosis. Thus, we concur with other authors that Armanni-Ebstein lesions are a feature of hypothermic deaths [5,6,8], but would also suggest that in some cases this may occur due to an association with diabetic ketoacidosis, rather than as a result of a significant reduction in body temperature *per se*. Thus when hypothermia is suspected at autopsy, specific enquiry should be made regarding a possible history of diabetes mellitus and vitreous humour should be tested for elevated glucose, β-hydroxybutyrate and lactate to determine whether there is biochemical evidence of underlying diabetic ketoacidosis.

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